

AWARD NUMBER: CDMRP-16-0-DM167040

TITLE: Preclinical Evaluation of the Effects of Aeromedical Evacuation on Military-Relevant Casualties

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REPORT DATE: October 2017

TYPE OF REPORT: ANNUAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE OCT 2017		2. REPORT TYPE ANNUAL		3. DATES COVERED 1 Oct 2016 - 30 Sep 2017	
4. TITLE AND SUBTITLE Preclinical Evaluation of the Effects of Aeromedical Evacuation on Military-Relevant Casualties				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER CDMRP-16-0-DM167040	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Richard McCarron, Dr. Anke Scultetus E-Mail: Richard.m.mccarron.civ@mail.mil ; anke.h.scultetus2.civ@mail.mil				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
				8. PERFORMING ORGANIZATION REPORT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Medical Research Center Silver Spring, MD 20910					
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Current practice in Operation Enduring Freedom commonly includes transport of the critically injured patient to the Continental United States (CONUS) soon after stabilization and initial surgery. In general, service members can be returned to the US medical treatment facility in five-to-seven days. Aeromedical transport is associated with obvious concerns that include hypobaria, hypoxemia, air trapped within a body cavity, vibration, and hypothermia. Current guidelines for critical care air transport teams (CCATT) note that basic physiology parameters during transport are to be supported; to include adequate oxygen saturation, ventilation, blood pressure etc. However, these parameters may be difficult to achieve. The impact of hypobaria on the transport of critically ill patients is unknown. Applying resuscitation guidelines for trauma developed over decades for ground-based scenarios to aeromedical transport is simply based on expert opinion. This grant incorporates three projects that address specific operational issues regarding optimization of aeromedical evacuation standards. In animal models of combat trauma, we will address the effects of timing, altitude, and oxygen supplementation during aeromedical evacuation.					
15. SUBJECT TERMS None listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

Current practice in Operation Enduring Freedom commonly includes transport of the critically injured patient to the Continental United States (CONUS) soon after stabilization and initial surgery. In general, service members can be returned to the US medical treatment facility in five-to-seven days. Aeromedical transport is associated with obvious concerns that include hypobaria, hypoxemia, air trapped within a body cavity, vibration, and hypothermia. Current guidelines for critical care air transport teams (CCATT) note that basic physiology parameters during transport are to be supported; to include adequate oxygen saturation, ventilation, blood pressure etc. However, these parameters may be difficult to achieve. The impact of hypobaria on the transport of critically ill patients is unknown. Applying resuscitation guidelines for trauma developed over decades for ground-based scenarios to aeromedical transport is simply based on expert opinion.

This grant incorporates three projects that address specific operational issues regarding optimization of aeromedical evacuation standards. In animal models of combat trauma, we will address the effects of timing, altitude, and oxygen supplementation during aeromedical evacuation. The Naval Medical Research Center (NMRC) offers a unique convergence of capabilities and expertise for En Route Care research, and in particular, aeromedical evacuation. NMRC has a strong track record of pre-clinical research in combat trauma, collaborations on pre-clinical studies of the effects of altitude, and an extensive in-house capability for hyper- and hypo-baric research.

Study Design:

The three proposed projects that will expand upon these ongoing efforts are:

Project 1: “Evaluation of the timing of aeromedical evacuation in rat and swine models of TBI and polytrauma” will investigate whether early vs delayed aeromedical evacuation is optimal for patient outcome. It is subdivided into two phases. Phase 1: The specific aim is to evaluate the effects of aeromedical evacuation during standard (3 days after injury) vs. delayed transport (day 7, 10 or 14) of injured rats. Brain and lung injury will be induced in rats by exposure to a standard blast overpressure (BOP). Rats will be randomized to “day of transport” groups. Half of each group will be exposed to hypobaria equivalent to 8000 ft. altitude for six hours; half (controls) will be treated similarly except that the chamber will remain normobaric. An additional (sham) group will not receive a BOP-exposure; half will be exposed to hypobaria, half to normobaria. Animals will be euthanized for tissue samples on day 2, 8, or 30 following hypobaric exposure. Outcome measures will be neurocognitive testing, brain and lung gross and histopathology, and blood markers of immunological responses to injury. Phase 2: The specific aim is to evaluate the effects of aeromedical evacuation during a delayed transport (worst outcome from Phase 1) vs. standard transport of an injured swine on acute physiology end-points and histologic markers of injury. Instrumented swine with polytrauma [TBI, hemorrhagic shock (HS), and acute respiratory distress syndrome (ARDS)] will be resuscitated and exposed to hypobaria (8000 ft x 6 hrs), or normobaria (controls) on day 3 or a day down-selected from Phase 1 results. A sham group will be similarly exposed to hypobaria or normobaria, but without injury or instrumentation. Animals will be euthanized 48 hours after hypobaric exposure for necropsy and tissue collection. Endpoints include neurophysiological/physiological monitoring, gross and histopathology, and hematology.

Project 2: “The effects of oxygen supplementation during aero-medical evacuation on brain oxygenation in swine with fluid-percussion (FP) - TBI” specifically aims to determine the effects of O₂ supplementation during aeromedical evacuation in a swine TBI model. Post-injury, swine will be resuscitated and exposed to hypobaria (8000 ft. x 4 hrs) or normobaria (controls), with 30%, 50%, or 100% O₂ supplementation. Sham animals will be instrumented and exposed to hypobaria or normobaria. Animals will be euthanized for necropsy and tissue collection following hypobaric exposure. Outcome measures will be brain tissue oxygenation, neurophysiological and cardiopulmonary parameters, blood chemistry, and gross and histopathology.

Project 3: “Physiological consequences of 4,000 and 8,000 ft. altitude aeromedical evacuation on swine with TBI and hemorrhagic shock” will investigate the effects of hypobaria on injured swine evacuated at 8,000 vs. 4,000 ft altitude. The specific aims are to determine if (a) there are differences in the cardiac, pulmonary, and neurologic effects of a 4 hr aeromedical evacuation at 4,000 ft. vs 8,000 ft. on injured swine, and (b) the type and severity of injury is affected by altitude. Instrumented swine with TBI alone or TBI + HS, will be exposed to hypobaria equivalent (8000 ft. or 4000 ft. altitude), or normobaria (controls). The timeline will be identical to that used in Project (A)/Phase 2, but TBI and HS will be more severe, enabling groups from that study to be used as injury-severity comparators. Outcome measures will be similar to those for Project (A)/Phase 2.

This proposal aims to provide a knowledge base for optimizing En Route Care operational planning and clinical guidelines to improve functional outcomes of wounded warriors.

2. KEYWORDS: hypobaria, aeromedical evacuation, traumatic brain injury, lung injury, hemorrhagic shock, effects of flight, oxygenation, altitude, timing of evacuation

3. ACCOMPLISHMENTS:

During this reporting period, we secured IACUC approval for proposed animal work on the first two projects. ACURO approval is pending. No animal work will begin until ACURO approval has been secured.

WRAIR/NMRC IACUC protocol 17-OUMD-24LS “The Effects of Oxygen Supplementation During Aeromedical Evacuation on Brain Oxygenation in Swine with Fluid-Percussion (FP) - Traumatic Brain Injury (TBI)” (Project 2).

WRAIR/NMRC IACUC protocol 17-OUMD-29LS “Evaluation of the Timing of Aeromedical Evacuation in Rat and Swine Models of TBI and Polytrauma” (Project 1).

This is a 5-year grant and project 3 (Physiological Consequences of 4,000 and 8,000 ft. Altitude Aeromedical Evacuation on Swine with Traumatic Brain Injury and Hemorrhagic Shock) will not begin until FY19, therefore, not IACUC protocol has been submitted at this point.

During the next reporting period we plan to utilize the altitude environment capabilities of the Center for Hypobaric Experimentation, Simulation and Testing (CHEST) at Naval Medical Research Center to 1) evaluate the timing of aeromedical transport on end organ physiology and tissue damage in a rat blast model of TBI and lung injury and a swine model of TBI and hemorrhage and 2) initiate and conduct swine experiments aimed at defining an adequate oxygen supplementation level for aeromedical transport of polytrauma swine with both blood

loss and moderate TBI. Data will improve our knowledge of the effects of oxygen supplementation during aeromedical transport on the neurophysiology (i.e., brain oxygenation) of wounded troops and may assist in altering guidelines on oxygen supplementation.

4. IMPACT:

Research is needed to address knowledge gaps during long range patient transport to definitive care in the U.S. There is no data available about the impact of hypobaria on vital organ function in TBI and polytrauma patients. This proposal aims to provide a knowledge base for optimizing En Route Care operational planning and clinical guidelines to improve functional outcomes of wounded warriors. The knowledge gained will be used to optimize care is provided to our wounded service members as they are moved through the system. The proposed research will provide needed data on the impact of hypobaria on neurotrauma and polytrauma casualties and identify possible safety risks associated with aero-medical evacuation of such patients. This study will directly address improvement of combat casualty safety, morbidity and mortality.

5. CHANGES/PROBLEMS:

The hypobaric chamber designed and built at NMRC for this project is unique and there is no comparable device available to achieve the proposed research goals. A massive building renovation where the chamber is housed resulted in delays and challenges that could not be anticipated and have therefore not started animal experiments yet. We are currently in the process of building a second chamber to increase work power and efficiency at no cost to this grant and we do not foresee a delay in the overall grant schedule at this time.

6. PRODUCTS:

Technologies or techniques: N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Key Personnel:

McCarron, Richard, PhD; Site-PI(10% work effort-1.2 calendar months): Scientific oversight of the overall project, timely execution of tasks; advising on data interpretation and coordination of research efforts with other projects. Primary experience with neuroscience and TBI. (No salary requested)

Ahlers, Stephen, PhD; Project Co-PI(5% work effort-0.6 calendar months): Provides scientific expertise in the area of traumatic brain injury and neuropsychology. Additionally will be responsible for the design of the blast exposure study and its execution and management to include coordination of all participants, oversight of data interpretation and manuscript preparation. (No salary requested).

Col Debra Malone, MC, USAF; Project PI(5% work effort-0.6 calendar months): Trauma Research Director/Trauma and General Surgeon/Critical Care Physician, Walter Reed National Military Medical Center, Bethesda, MD, Member, Theater Infectious Disease Outcomes Study (TIDOS)

Scultetus, Anke, MD; Project PI(30% work effort-3.6 calendar months): Overall research program management with responsibility to plan, coordinate, and execute large and small animal experiments in models of Traumatic Brain Injury (TBI); collect physiological data and histopathological analysis obtained from animal experiments and prepare reports; interpret data and make adequate changes for subsequent experimental design, preparation of data for publication in journals or for presentations to peer groups. Coordinate database management, scientific publications, IND enabling pre-clinical studies, technical writing. Supervises implementation of GLP practices, as necessary, in laboratory, and maintenance of GLP-compliant training program.

Arnaud, Francoise, PhD; Project PI(10% work effort-1.2 calendar months): Perform research efforts in polytrauma to include Traumatic Brain Injury (TBI) resuscitation effects. Coordinate efforts of technicians and research assistants. responsible for comprehensive hematological analysis of data collected in large and small animal experiments in models of polytrauma (TBI and HS) and hemorrhagic shock (HS) studies; perform coagulation related experiments to assess responses to polytrauma; interpret data and make adequate changes for subsequent experimental design, prepare data for publication in journals or for presentations to peer groups.

Mahon, Richard, MD; Project Co-PI(5% work effort-0.6 calendar months): Dr. Mahon is a board certified pulmonologist and critical care specialist with extensive experience with swine models of ARDS and pulmonary oxygen toxicity. Furthermore Dr. Mahon is a well-known subject matter expert in the field of hypobaria and has served in such capacity for NASA and the DOD. Dr. Mahon will be responsible for study design, clinical relevance, and preparation of the data for publication in journals or presentation of findings to study sponsors and the wider scientific community. This is a part-time position (tier 2).

Other Personnel (all employees of the Henry M. Jackson Foundation):

Biswajit Saha, MD, Research Associate (50% work effort-6.0 calendar months): Will provide statistical analysis plan and perform statistical analysis.

Noemy Carballo, Neda Ilieva, Meghan Patterson, Jordan Hubbell, Andrea White; Research Assistants Physiology (50% effort- 6.0 calendar months each): Will conduct animal experiments; performs physiology/animal husbandry duties; maintain all equipment and supplies; preserve laboratory safety and scientific quality compliance.

Michael Hammett, Research Assistant Hematology (15% effort-1.8 calendar months): Will perform hematology assays and provide data analysis.

Ye Chen, MD, Scientist, Immunology (15% effort-1.8 calendar months): Will perform immunology assays and provide data analysis.

William Porter, Chamber Engineer (15% effort-1.8 calendar months): Engineering support; operates chamber during experiments; performs chamber maintenance; designed and built existing hypobaric chambers and will add vibration capability; applies many years of experience in building, maintaining and operating multiple hyperbaric chambers in the Undersea Medicine Department at NMRC.

Collaborations:

We are collaborating with Dr. Joseph McCabe, Department of Anatomy and Physiology at the Uniformed Services University (USU) on this project. He and his laboratory will provide support for histopathological analysis of samples.

8. SPECIAL REPORTING REQUIREMENTS:

Quad Chart Project 1:

Evaluation of the Timing of Aeromedical Evacuation in Rat and Swine Models of TBI and Polytrauma

Joint En Route Care Award - Intramural

Log Number DM167040 - Project 1

PI: Dr. Anke H. Sautter, Dr. Stephen T. Atiles. Org: NMRC/USUHS Award Amount: \$1,176,000



Study/Product Aim(s)

- This proposal aims to clarify appropriate timing for altitude transport based on whole animal physiology, regional organ perfusion, inflammatory markers and tissue damage.
- We hypothesize that long range aeromedical transport of trauma victims effects specific organ blood flow, inflammation and histological markers of tissue damage and that these endpoints can be modified by the timing of altitude transport.

Approach

We propose to investigate the relationship between standard versus delayed aeromedical evacuation and possible influences on patient outcome in a realistic combat casualty care, evacuation and definitive care study in rats and swine. Rats will receive one 120 kPa blast; swine will receive TBI or ARDS. Animals will undergo aeromedical evacuation on day 3 after injury (standard), or they will be on a delayed transport schedule of 7, 10 or 14 days.



Rapid evacuation of combat casualties to CONUS is current standard. However, our lab showed that hypoxia reduces brain tissue oxygenation in TBI swine. This study will evaluate the effects of the timing of evacuation.

Timeline and Total Cost

Activities	FY	17	18	19	20	21
IACUC/ACURO approval						
Rat blast/Alt timing experiments						
Swine TBI/polytrauma Alt timing experiments						
Data analysis, final report, manuscript preparation						
Estimated Total Budget (\$K)		181	179	200	200	416

Goals/Milestones

- FY17 Goals
 - X IACUC/ACURO protocol written, submitted and approved
- FY18 Goals
 - Begin rat blast experiments
 - Complete rat blast experiments
- FY19 Goals
 - Initiate swine TBI experiments
 - Initiate swine ARDS experiments
 - Data analysis rat study
- FY20 Goals
 - Continue swine experiments
- FY21 Goals
 - Complete swine experiments
 - Data analysis swine study
 - Manuscript preparation and final study report
- Comments/Challenges/Issues/Concerns: None
- Budget Expenditure to Date: \$175K

Updated: \$10CT17

Quad Chart Project 2:

The Effects of Oxygen Supplementation During Aeromedical Evacuation on Brain Oxygenation in Swine with Fluid-Percussion (FP) - Traumatic Brain Injury (TBI)

Joint En Route Care Award - Intramural

Log Number DM167040 - Project 2

PI: Dr. Françoise Areaud, Dr. Richard Mahon. Org: NMRC/USUHS Award Amount: \$577,610



Study/Product Aim(s)

- We hypothesize that hypoxia during simulated long range aeromedical evacuation has adverse effects on brain blood flow, lung function and tissue oxygenation in neurotrauma and polytrauma patients.
- In a swine model, we plan to test the hypothesis that adapted supplementation with oxygen will be beneficial to the wounded during hypobaric aeromedical evacuation.

Approach

In a polytrauma swine model combining traumatic brain injury (TBI) and hemorrhage (HS), animal physiology, and metabolic, immunologic and histologic markers of injury will be evaluated at three supplemental oxygen levels (FIO₂ of 30, 50 and 100%) during simulated altitude transport at 8,000 ft., 2 hours after injury. In flight conditions will be reproduced in a hypobaric chamber at NMRC. A total of 62 swine are needed to conduct this research.



Severely wounded are often aero evacuated with 100% oxygen supplementation. The benefit of this strategy to brain and organ function is unknown. This study evaluates 3 levels of oxygen supplementation (30, 50 and 100%) particularly on tissue oxygenation using a pre-clinical polytrauma swine model.

Timeline and Total Cost

Activities	FY	17	18	19	20	21
IACUC/ACURO approval						
Swine supplemental O ₂ /AE experiments						
Data analysis, final report, manuscript preparation						
Estimated Total Budget (\$K)		53	268	217	40	

Goals/Milestones:

- FY17 Goal - IACUC/ACURO protocol approval
- X Write and submit protocol - Get approval
- Initiate supplemental O₂ /AE experiments
- FY18/19 Goals - Swine supplemental O₂ /AE experiments
 - Finalize Normo and Hypo settings
 - Complete oxygen supplement under normo and hypobaric
 - Collect physiology and laboratory data
 - Start analyzing data
- FY20 Goal - Complete project
- Data analysis
- Write report
- Write - Submit manuscripts
- Comments/Challenges/Issues/Concerns: None
- Budget Expenditure to Date: \$40K

Updated: \$10CT17

Quad Chart Project 3:

Physiological Consequences of 4,000 and 8,000 ft. Altitude Aeromedical Evacuation on Swine with Traumatic Brain Injury and Hemorrhagic Shock

Joint En Route Care Award – Intramural

Log Number DM167040 – Project 3

PI: Col Debra Malone, MC, USAF, Dr. Anke H. Sautels Org: NMRC/USHS Award Amount: \$919,539



Study/Product Aim(s)

- Determine if there are differences in the neurologic, cardiac, and pulmonary effects of a 4 h transport at 4,000 ft. vs. 8,000 ft. on casualties with TBI or TBI + hemorrhagic shock (HS).
- Determine if the type and severity of the injury (TBI or TBI + HS) is affected by altitude.

Approach

Animals will undergo TBI, TBI + HS, or Sham (no injury) and, after a 90 min stabilization period, will be exposed to one of three simulated transport altitudes (0, 4,000 or 8,000 ft.) for 4 h using a hypobaric chamber. TBI will be a fluid percussion injury of moderate severity (3.5 atm.) to allow comparison with previous studies; and HS will be induced by loss of 40% of blood volume.



US Navy combat nurse Lt. Cdr. Eric Gryn tends to a critically injured civilian en route to hospital. The hypobaric chamber at the new Center for Hypobaric Experimentation, Simulation and Testing (CHESST) will simulate such transport in swine. It has been successfully used for two swine studies in 2016.

Timeline and Total Cost

Activities	FY	17	18	19	20	21
IACUC/ACURO approval						
Swine Aeromedical Evacuation / Altitude experiments						
Data analysis, final report, manuscript preparation						
Estimated Total Budget (\$K)				257	229	334

Goals/Milestones:

FY18 Goal – IACUC/ACURO approval and begin air evac altitude experiments

- X IACUC/ACURO protocol written, submitted and approved
- o Pilot animals (N = 5) for technique and system verification
- o Begin in-life experiments (N = 72)

FY20 Goals – Complete air evac altitude experiments

- o Complete in-life experiments (N = 72)
- o Batched biosamples analyzed and Histopathology
- o Final database (Cleaned and loaded)
- o Statistical Analysis

FY21 Goal – Publication

- o Manuscript preparation and submission

Comments/Challenges/Issues/Concerns: None
Budget Expenditure to Date: \$0K

Updated: 31OCT17

9. APPENDICES:

None.